Albuterol Inhalation Aerosol
ANDA #73-045
Alpharma

Index of Supporting Documents

1) Repeat Cascade Impactor Study on lot 8457 including tables of weights, mcg of drug collected at each stage, representative chromatograms, and a two page spreadsheet of tabulated and graphic presentation of results. The method used to perform the study is also attached for convenience.

2) Batch record and certificate of analysis for lot 8457.

3) Explanation of typographical errors (as discussed during 9/9/96 meeting).

4) Validation Data for Method - This validation was already submitted in an amendment to the application dated September 11, 1996. Included in this validation report are definitions of terms, table headers, dilution volumes. LOQ (limit of quantitation) determination is included as attachment 4 in this amendment.

5) Tabular and graphic representation of the original and repeated cascade impaction testing of expired lots 6403 (test) and 231383LS (Ventolin® reference) from the clinical study.

BIOAVAILABILITY

ALPHARMA™
U.S. Pharmaceuticals Division

September 30, 1996

NDA ORIG AMENDMENT

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application dated December 23, 1988. Reference is made to the September 25, 1996 FDA correspondence (attached) pertaining to the analytical methods validation. Reference is also made to the FDA correspondence of 7/18/96 and 9/3/96 and to our correspondence dated 6/12/95, 8/1/96, and 9/9/96.

We trust that we have addressed the Agency's concerns.

Sincerely,

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GENERIC DRUGS

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure

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Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax. (410) 558-7258

ALPHARMA™
U.S. Pharmaceuticals Division

September 20, 1996

NDA ORIG AMENDMENT
N/AF FPL

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application dated December 23, 1988. Reference is made to the September 3, 1996 FDA correspondence pertaining to drug product labeling (attached) and to our amendment dated 8/1/95 containing the drug product insert.

The drug product insert labeling has been revised as requested. Twelve copies of final printed inserts are enclosed (page 2). A side-by-side labeling comparison between the revised insert and the insert previously submitted as page 07 of the 8/1/95 amendment to the application is enclosed as pages 3-8 and annotated differences are contained on page 9.

We trust that we have addressed the Agency's concerns.

Sincerely,

Deborah Miran
Sr. Director, Regulatory Affairs

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U.S. Pharmaceuticals Division

NEW CORRESP

September 11, 1996

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Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

AMENDMENT TO AMENDMENT DATED SEPTEMBER 9, 1996

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the amendment dated September 9, 1996 pertaining to bioequivalence issues. Reference is made to the September 3, 1996 FDA correspondence pertaining to the bioequivalence study and to our response of September 9, 1996.

A review of the listing of all the data necessary to calculate PD_{20}s revealed that data for one methacholine challenge was inadvertently omitted from the September 9, 1996 amendment to the bioequivalence study. The missing data are the pre-albuterol (morning) methacholine challenge data for subject 116 on the first visit (11/09/94). These data are provided on page 2 and are part of Tables 3 and 4 of the September 9, 1996 amendment to the bioequivalence study. These data have been added onto a diskette along with the data previously supplied in the September 9, 1996 bioequivalence amendment and the updated diskette is provided now.

In addition, based on comments from the September 9, 1996 meeting between representatives of the Office of Generic Drugs and Alpharma pertaining to the Cascade Impaction particle size test, we supply the following information.

> Analytical methods validation for the Cascade Impaction particle size test method (pages 3-46). This validation report was previously submitted to the application as pages 168-211 of the 12/2/94 amendment to the application and pages 030-073 of the 8/1/96 bioequivalence amendment.

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Cascade Impaction particle size (continued)

Definitions for symbols in tables (based upon USP 23):

Pages 002-003 of the 8/1/96 bioequivalence amendment (same tables are on pages 095-098 of the 8/1/96 bioequivalence amendment):

A= Total mass of drug delivered from the actuator.

C= Total mass of drug collected (from stem through final impactor stage).

D= Expected mass of drug to have been delivered (mass of formulation delivered times concentration of drug in formulation).

Pages 101 and 103 of the 9/9/96 bioequivalence amendment:

A= Total mass of drug delivered from the actuator.

C= Total mass of drug collected (from stem through final impactor stage).

D= Expected mass of drug to have been delivered (mass of formulation delivered times concentration of drug in formulation).

Dilutions volumes for drug collected:

Pages 002-003 of the 8/1/96 bioequivalence amendment (same tables are on pages 095-098 of the 8/1/96 bioequivalence amendment):

Actuator: mL.
Induction port: mL.

Pages 004-005 of the 8/1/96 bioequivalence amendment (same tables are on pages 565 and 567 of the 6/12/95 bioequivalence submission):

Stages mL.
Filter: mL.

Pages 101 and 103 of the 9/9/96 bioequivalence amendment:

Actuator: mL.
Induction port: mL.

Pages 100 and 102 of the 9/9/96 bioequivalence amendment:

Stages mL.
Filter: mL.

We trust that we have addressed the Agency's concerns.

Sincerely,

Alpharma
Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure

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ALPHARMA™
U.S. Pharmaceuticals Division

NDA ORIG AMENDMENT
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September 5, 1996

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GENERIC DRUGS

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), Alpharma, U.S. Pharmaceuticals Division submits an amendment to the above referenced application. Reference is made to the August 23, 1996 teleconference between Ms. Sheila O'Keefe (FDA, OGD) and myself concerning drug product methods validation and to our drug application dated 12/23/88. Reference is also made to the Agency's correspondence of 7/21/91, 6/3/94, 8/11/94, 5/26/95, 1/29/96, 4/8/96, 7/18/96, and 8/22/96 and to Alpharma's correspondence of 2/4/94, 2/14/94, 12/2/94, 1/27/95, 6/12/95, 6/22/95, 8/1/95, 2/23/96, 5/1/96, 8/1/96, and 8/22/96.

The Agency's comments from the 8/23/96 teleconference and telefax (attached) have been summarized and our responses follow.

General comments

All methods
Alpharma acknowledges that all methods except the Unit Dose/Content Uniformity method are acceptable for FDA regulatory and quality control procedures.

Total number of actuations per canister
The method for Total Number of Actuations per canister has been revised to utilize a minimum actuation weight as a measure of the total number of actuations in a can.

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Unit Dose/Content Uniformity
Based on an August 27, 1996 teleconference with Dr. Mike Smela (FDA, OGD), Alpharma has requested that the Unit Dose/Content Uniformity testing be re-performed by the FDA testing laboratory using the methods filed in the application (ie., company's apparatus and 30 L/min flow rate). Alpharma has been in contact with FDA's St. Louis laboratory, and the re-testing will be performed on September 12 and 13, 1996. Qualified personnel from Alpharma and CCL Industries (the testing laboratory within the application) will be present when the retesting is performed.

1. **Assay For Entire Canister Content**
The analytical methods have been revised (pages 04-06 for release, pages 08-10 for stability). A summary of the changes precede each method (pages 02-03 and 07, respectively). The use of dry ice as a means to freeze the cans has been added; the tool for cutting open the cans has been more clearly specified; and the procedure for rinsing the contents from the can has been more clearly specified.

2. **Spray Pattern**
The analytical methods have been revised (page 12 for release, page 14 for stability). A summary of the changes precede each method (page 11 and 13, respectively). The designation for the plate was corrected; the time interval for shaking between sprays was added; and the type of UV light for viewing the spots was identified.

3. **Albuterol Related Substances**
The analytical methods have been revised (pages 18-22 for release, pages 24-28 for stability). A summary of the changes precede each method (pages 15-17 and 23, respectively). Differences between the quality control test method and the stability test method were eliminated (standard preparation; can freezing; placebo testing; and system suitability tests); the number of standard injections for the system suitability test was increased to 6; the method for opening the cans was revised to cutting off the valve; the test for Coefficient of Variance was deleted and the test for Relative Standard Deviation was added; instructions have been added as to which peaks are to be used to determine the system suitability; the definition of symbol has been moved to the unknown impurities calculation; the symbol has been defined as the impurity peak in the "ethanol" impurity calculation; the symbol "Wspl" has been defined as an average weight; and in the unknown impurities calculation, the symbol "Rn" has been defined as all peaks excluding albuterol and placebo peaks.

4. Content Uniformity

The analytical methods have been revised (pages 30-34 for release, pages 36-40 for stability). A summary of the changes precede each method (page 29 and 35, respectively). Differences between the quality control test method and the stability test method were eliminated (limits for system suitability tests; and calculations utilize standard potency correction); system suitability tests were revised to require 6 injections; the instructions for the standard comparison were corrected; the designation of the Appendix was corrected; dimensions have been added to the diagram of the sampling apparatus; the volume of absorbing solution was left at 25 mL. It is not necessary to cover the frit during this procedure. As long as the absorbing solution is in contact with the frit, capillary action will draw liquid up onto the frit. The wetted frit will then allow the aerosol spray to be captured. The weight of each collected spray is now recorded for performance of the shot weight test; RSDs of less than 3 are a requirement to assure that the chromatographic system is operating properly; and a conversion calculation between weight and percent has been added.

5. Shot Weight

The test for Shot Weight has been added into the Quality Control test method for Unit Spray Content & Total Number of Shots Per Can (GS052) (pages 43-47). A revised Product Specification incorporating the Shot Weight test and specification is enclosed as pages 54-57. The previous revision of this document is located on pages 45-47 of the 8/1/95 amendment to the application.

6. Total # Of Shots

The analytical methods have been revised (pages 43-47 for release, pages 49-53 for stability). A summary of the changes precede each method (pages 41-42 and 48, respectively). The Total Number of Shots test is part of the Unit Spray Content test method. The procedure was revised to indicate that the Total Number of Shots is reached when the shot weight drops below 77 mg/spray.

7A. Cascade Impaction By Andersen Cascade Impactor

The analytical methods have been revised (pages 60-64 for release, pages 72-76 for stability). A summary of the changes precede each method (pages 58-59 and 65, respectively). The term "USP was added to the throat/induction port portion of the impactor drawing, signifying USP dimensions; The airflow was revised to "28.3 +/- 0.6 liters/minute" to match the manufacturer's calibrated parameters; the two parts of the induction port (induction port and top cone) have been identified; the type and

manufacturer of the filter , have been added at the end of the Sample Preparation section and to the apparatus drawing; the number of standard injections for the system suitability tests was increased to 6; weighing of the cans was added into the Sample Preparation section of the Quality Control method; rinsing of the valve stem has been added to the Sample Preparation section; a calculation for mcg albuterol per stage has been added to the Quality Control method; and reference to the SOP for calculation of results was added into the Quality Control and Stability test methods.

For the procedure for interpreting results (pages 65-68), no specifications have been established for GSD since this is tabulated for informational purposes only; the calculation for MMAD has been reworded (Calculations for %LT 5 and %LT 10 μm have been deleted); the calculation for Mass Balance is the calculation for Total Recovery; specifications of % for Total Recovery have been added; the term "amount retained" pertains to the quantity of drug retained on the actuator; the Total Recovery calculation was revised to not utilize the theoretical content per shot value; and the term "oral adapter" is synonymous with the actuator.

7B. Particle Size Determination By Twin Impinger Type II

The analytical methods have been revised (pages 79-83 for release, pages 85-89 for stability). A summary of the changes precede each method (pages 77-78 and 84, repectively). The procedure was revised to require shaking between shots discharged to waste; Relative Standard Deviation has been added as a system suitability test; the Shot Weight calculation was deleted since it is not utilized in any calculation; calculations for Stage 1 and actuator deposition are determined for informational purposes only, therefore limits have not been specified; and the retention time window and mobile phase adjustment were deleted from the method.

8. Unit Spray Content

The analytical methods have been revised (pages for release, pages for stability). A summary of the changes precede each method. Differences between the release and stability methods have been eliminated (3 cans are tested; priming process; and collected sprays); as discussed for Total Number of Shots above, the procedure was revised to indicate that the Total Number of Shots is reached when the shot weight drops below 77 mg/spray; the number of units to be sampled is 3; and sprays 10-11 are collected.

Pursuant to 21 CFR 314.96(b), Alpharma certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

We trust that we have addressed the Agency's concerns.

Sincerely,
Alpharma

Ronald Bynum /for

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure

ALPHARMA
U.S. Pharmaceuticals Division

August 30, 1996

NEW CORRESP
NC

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA #73-045
Albuterol Inhalation Aerosol

TRANSFER OF OWNERSHIP OF A PENDING APPLICATION

Dear Mr. Sporn:

On June 20, 1996 Alpharma, U.S. Pharmaceuticals Division acquired the ownership of, and all right, title and interest of any nature in the above-referenced abbreviated new drug application. In accordance with 21 CFR § 314.72(a)(2), we are notifying the Food and Drug Administration of transfer of ownership from Barre-National Inc., 333 Cassell Drive, Suite 3500, Baltimore, Maryland 21224. Barre/NMC have been wholly owned subsidiaries of Alpharma USPD. On Thursday, June 20, 1996, as the attached notice indicates, the company name was changed to Alpharma, USPD, Inc. Accordingly, we are transferring ownership to the new company name.

Enclosed is a completed, signed Form FDA-356H specifying Alpharma, U.S. Pharmaceuticals Division as the applicant.

Sincerely,
ALPHARMA

Deborah Miran
Sr. Director, Regulatory Affairs

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Enclosures

Research & Development Center
The Johns Hopkins Bayview Campus, 333 Cassell Drive, Suite 3500, Baltimore, MD 21224
Tel: (410) 558-7250 Fax: (410) 558-7262

A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
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NDA ORIG AMENDMENT
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August 22, 1996

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GENERIC DRUGS

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

TELEPHONE AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), A. L. Laboratories (now known as Alpharma) submits an amendment to the above referenced application. Reference is made to the August 22, 1996 teleconference between Dr. Michael Smela (FDA, OGD) and myself concerning drug product specifications and to our drug application dated 12/23/88. Reference is also made to the Agency's correspondence of 7/21/91, 6/3/94, 8/11/94, 5/26/95, 1/29/96, 4/8/96, and 7/18/96 and to A.L. Laboratories' correspondence of 2/4/94, 2/14/94, 12/2/94, 1/27/95, 6/12/95, 6/22/95, 8/1/95, 2/23/96, 5/1/96, and 8/1/96.

The Agency's comments from the 8/22/96 teleconference have been restated and our responses follow.

1. **Please add the Shot Weight test to the drug product release specifications.**

   As agreed to during today's teleconference between Dr. Smela and myself, A.L. Laboratories commits to adding the Shot Weight test to the drug product release specifications. The revised specifications document will be submitted to the application post-approval.

The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500 • Baltimore, Maryland 21224
Telephone: 410 558-7250 • Fax: 410 558-7258

2. Please provide a copy of the current drug product release and stability specifications and the drug substance specifications.

The drug product release specifications (Product specification) are enclosed on pages 2-4. These specifications were previously submitted as pages 45-47 of the 8/1/95 amendment to the application.

The current drug product stability specifications (Stability Monograph) are enclosed as pages 5-6. These specifications differ from the specifications previously submitted as pages 48-49 of the 8/1/95 amendment to the application in that the Laser Diffraction particle size test method has been deleted per our 12/2/94 response to question #4d (attached as page 7).

The drug substance specifications are enclosed on pages 8-9. These specifications were previously submitted as pages 289-290 of the 12/2/94 amendment to the application.

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

We trust that we have addressed the Agency's concerns.

Sincerely,
A.L. Laboratories, Inc.

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

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August 1, 1996

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), A. L. Laboratories (now known as Alpharma) submits an amendment to the above referenced application. Reference is made to the Agency's letter dated July 18, 1996 (attached), regarding our Abbreviated New Drug Application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and to our June 12, 1995 in vitro data submission for bioequivalence.

The Agency's comments have been restated and our responses follow.

1. **The June 12, 1995 *in vitro* data submission, Vol A8.2, provides particle size data by cascade impactor; pages 565 and 567 lists amounts of drug deposited on various stages of the impactor. Complete mass data on laboratory worksheets for each of the 18 studies for test and reference products, including amount of drug on the valve, actuator, and atomizing chamber should be provided, and also each date study was performed. Please provide legible representative plots of these studies showing the computation of MMAD and GSD.**

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Data for drug collected on the actuator and the induction port are tabulated on pages 002 and 003. Mass balance (C) is also included. Data for drug collected on the various stages and filter were previously submitted as pages 565 and 567 of the 6/12/95 submission (pages 004 and 005 of this amendment). These charts represent complete mass data.

We do not assay the residue of drug from the valve stem as part of our analytical method, and as such, the material balance percentage has been calculated without this. We have, however, performed testing to ascertain the amount of drug actually retained on the valve and the impact of this on the material balance. The amount retained on the valve stem equated to approximately µg/spray (page 024). This equates to µg over 25 sprays (as used in cascade impactor testing) and approximately % of the material balance percentage, which is negligible.

Dates of analysis are as follows:

Ventolin®, lot# Z31383LS: February 16, 1994.
Albuterol, lot# 6403: February 18, 1994.

Representative plots showing computation of MMAD and GSD are enclosed as pages 006 to 023.

2. **The Andersen cascade impactor is calibrated at L/minute. The firm used a flow-rate of 30 L/minute. USP 23 <601> specifies that the flow-rate through the cascade impactor should be within 2% of that specified by the manufacturer. Please comment. Please state the model number of the cascade impactor.**

The cascade impactor data generated used a flow rate of 30 L/min and followed validated methodology. The methods validation was previously submitted as pages 163-211 of the 12/2/94 amendment to the application (pages 025 to 073 of this amendment).

As discussed below, the calculated differences between the 30 L/min flow rate and the L /min flow rate are negligible. Further, the Ruggedness section of the methods validation package (section 7) (page 041 of this amendment) contains data for flow rates from L/min, which is a greater deviation than between L/min, yet the results still show little difference.

The data produced for the in vitro data submission are comparative data between the test drug product (Albuterol) and the reference drug product (Ventolin®) and both sets were produced following the same methodology. This is a comparative test, therefore, the absolute values are not significant, whereas, comparability is significant. Therefore, the data produced with the 30 L/min flow rate are acceptable.

In order to critically assess the difference due to utilization of the 30 L/min flow rate rather than the L/min flow rate, the cut-off diameters have been recalculated based on a flow rate of 30 L/min. The formula for the calculation and the cut-off diameters are listed on page 074. It was concluded that the difference in flow rate had no significant effect on particle size results. All sets of data were re-plotted and the results are provided on page 075. The results of the recalculated data are very similar to those of the original data (pages 004 and 005). Plots of the recalculated data are provided on pages 076 to 094.

The model number of the cascade impactor utilized in the testing is Andersen 1ACFM Non-viable Ambient Particle Sizing Sampler (Mark II).

3. **Cascade impactor validation tests in Volume 7.1, "Drug Product Specifications and Tests" are dated November 1994. Do these validation data apply to the comparative data summarized in Volume A8.2, pp. 565, 567?**

The validation tests in volume 7.1 (pages 163-211 of the 12/2/94 amendment to the application; pages 025 to 073 of this amendment) were performed on the same method as used for the analysis generating the comparative data summarized in volume A8.2 pg 565, 567 of the 6/12/95 in vitro data submission.

4. Please provide respirable dose and respirable fraction data based on drug less than microns for each cascade impactor study. These data should be computed as described in USP 23, <601>.

Respirable dose and respirable fraction data, based on particle sizes less than microns are tabulated in the tables on pages 095 and 096.

5. Percentage material balance as defined in USP 23 <601> should be provided for each cascade impactor study. The mass of formulation delivered and the concentration of drug in the formulation should also be provided, along with the quantities in each individual canister used to compute these average mass and concentration values.

Material balance percentage data are tabulated in the tables on pages 097 and 098. The calculation for the mass of drug expected to be delivered (D), has been calculated per USP 23 <601> (multiplying the mass of formulation delivered by the concentration of drug in the formulation). Since this calculation is a theoretical calculation (determination of an expected mass), the theoretical concentration of drug in the formulation, mg/g (see batch manufacturing formulation, page 100), was utilized in the calculation. This same value was used for both the test and reference drug products in order to provide comparative values. The mass of formulation delivered is tabulated on page 099. The total mass of drug collected (C), and the total mass of drug delivered from the mouthpiece (A), are tabulated on pages 097 and 098.

6. Regarding the batch record, please indicate the actual and theoretical batch size, including the number of filled canisters manufactured.

The theoretical batch size of the test drug product was units as stated on page 1 of 6 of the Manufacturing Document (page 630 of the 6/12/95 submission; page 100 of this amendment). For the submission batch, lot #6403, actual filled quantities can be found on page 5 of 12 of the Filling Document (page 650 of the 6/12/95 submission; page 101 of this amendment). The information is summarized below:

Pallet count:
Rejects:
Samples:
Total Units Filled:

Batch reconciliation is located on page 651 of the 6/12/95 submission (page 102 of this amendment). Accounting for quantity filled and quantity lost to waste due to flushing of the lines, there was a % loss for this batch.

7. **Please provide an explanation of the randomization process used to select test product canisters for the comparative *in vitro* bioequivalence testing, as well as for the *in vivo* bioequivalence study.**

For the test product, samples were collected from the beginning, middle, and end of the packaging run to assure representation of the entire batch. From these collected samples, random samples were taken for both the in-vitro testing and the in-vivo bioequivalence study. For the reference product, random samples of purchased product were utilized for both the in vitro and the *in vivo* testing.

8. **The formulation provided in volume 1.1, Section 5, p. 93, indicates an overage of % %). Please clarify whether the overage applies to drug only or to all ingredients. If to all ingredients, does the product include an additional overage of drug only?**

The overage in the formulation is a manufacturing filling overage and therefore applies to all ingredients. As noted on page 00093 of the 12/23/88 ANDA submission, this is to assure that the minimum of 200 declared sprays is achieved (page 103 of this amendment). The overage accounts for filling variability and assures that the metering chamber of the aerosol valve is completely covered during the entire 200 labeled sprays.

The drug product does not contain an additional overage of drug only.

9. **The Potency section of Volume A8.2 provides comparative data for only three canisters of test and reference products, instead of the ten canisters recommended by the 1989 *In Vitro* Guidance. In addition to estimation of mean drug delivery at beginning, middle and end of canister life, these ten canister data are also used to assure conformity to uniformity of unit spray content specifications (USP<905>). No conclusions can be drawn from the data of three canisters. The firm is requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration date of the products. The lot number of the reference listed drug does not correspond to that of the bioequivalence lot number. The firm is requested to confirm that these data were based on'**

We have been requested to provide comparative unit spray content for ten canisters of the test and ten canisters of the reference products used in the *in vivo* bioequivalence study, determined within the expiration date of the products. Unfortunately, additional testing within expiration dating is not possible. The test drug product is now 36 months old, 12 months past its tentative 24 months expiration date. The reference drug product expired in March, 1996.

Since the expressed concern is for assuring conformity to uniformity of unit spray content specifications (USP <905>), we can address this issue with content uniformity data from the stability program for the test drug product, lot #6403. Quantity of drug delivered per spray (µg/spray) and weight loss per spray (mg/spray) are provided. Analytical method was utilized to collect this data (pages 104 to 108). This method was previously submitted to the application as pages 13-17 of the 8/1/95 amendment to the application.

24 months room temperature test station, inverted, packed (with actuator) (page 109).

24 months room temperature test station, inverted, refill (without actuator) (page 110).

21 months room temperature test station, inverted, packed (with actuator) (page 111).

24 months room temperature test station, upright, packed (with actuator) (page 112).

24 months room temperature test station, upright, refill (without actuator) (page 113).

In addition, unit spray content data from the beginning, middle, and end of three cans is also provided from the stability program for the test drug product, lot #6403. Analytical method was utilized to collect this data (pages 114 to 118). This method was previously submitted to the application as pages 39-43 of the 8/1/95 amendment to the application.

24 months room temperature test station, inverted, packed (with actuator) (page 119).

24 months room temperature test station, inverted, refill (without actuator) (page 120).

21 months room temperature test station, inverted, packed (with actuator) (page 121).

24 months room temperature test station, upright, packed (with actuator) (page 122).

24 months room temperature test station, upright, refill (without actuator) (page 123).

This data, along with the potency data previously submitted on page 626 of the 6/12/95 submission (page 124 of this amendment) is sufficient to assure potency and content uniformity for the test drug product.

As mentioned before, additional testing of the reference drug product within expiration dating is not possible. This is not a critical issue since the question really concerns the test drug, which is the subject of this application. Since Ventolin® is already an approved drug product, its content uniformity has been established.

We can confirm that the lot number on the reference drug product potency summary sheet (page 627 of the 6/12/95 submission) was incorrect. The number should have read Z31383LS. A typographical error was made when the lot number was printed as Z3133LS.

We can confirm that the potency data in the 6/12/95 submission was obtained utilizing analytical method

10. Comparative spray pattern profiles are inadequate. Accurate measurements cannot be assured based on the photocopies provided in Volume A8.2, pp.619-620. In the experience of the Division of Bioequivalence, spray patterns from an inhalation aerosol do not exhibit the irregular patterns shown on pp. 619-20. Please provide photographs of the UV spots for review, along with a complete listing of the experimental procedure, including the number of actuations fired to waste between each experiment.

A recognized aerosol expert( ) was contacted concerning the spray pattern profiles and was asked to comment on the spray pattern shapes. It was opinion that the patterns are characteristic for metered dose aerosols and should not be deemed as "irregular".

Photographs of the spots previously provided as photocopies are not available since photography is not part of our analytical method. In our procedure, the spots are visualized under UV light. The outline of the spots are drawn by hand with a pencil and the plates are then photocopied to show the outline.

The Spray Pattern test method was previously submitted as pages 616-617 of the 6/12/95 submission (pages 125 and 126 of this amendment). It should be noted that the spots are visualized under UV light. The outline of the spots are then drawn by hand with a pencil and the plates are then photocopied to show the outline. This free-hand drawing contributes to the appearance of the patterns. It should be noted that no shots were fired to waste between experiments.

The shortest and longest diameters of the patterns were previously submitted as page 618 of the 6/12/95 submission (page 127 of this amendment). The narrow range between the shortest and longest diameters demonstrate that the patterns are essentially spherical (5 mm for the test drug product, 9 mm for the reference drug product). It should be noted that spray pattern testing performed by different laboratories produce patterns that are not superimposable due to differences in distances and angles utilized in the testing. Therefore, it is not unusual to see slight differences in spray pattern profiles produced by different companies.

TEST AND REFERENCE BLO BATCHES EXPIRED.

To further address the spray pattern issue, on or about July 26, 1996 we re-performed the spray pattern testing. Photographs of the resultant spots under UV light are provided as page 128. A photocopy of the plates showing the spots and the results for the shortest (min), the longest (max), and the mean (X) diameters are provided on pages 129 and 130. A table summarizing this new spray pattern data is provided as page 131. It should be noted that the results from the recent testing are very similar to those from the previous testing.

11. **Regarding the particle size distribution data by Malvern Laser, please provide information regarding the methodology (Volume A8.2, pp. 568-605) using [redacted] If this method for sizing aerosols is a standardized, validated method, please provide references and other relevant information. Please comment on the effect of spraying every two or five seconds, which is more frequent than the labeled interval between successive doses, on the resultant particle size distribution. Please comment on the effect of spraying with the canister held in a near-horizontal position rather than the labeled near-vertical position.**

The method and subsequent validation have previously been submitted as pages 426-455 of the 2/4/94 amendment to the application (pages 132 to 161 of this amendment). This method for particle size measurement is non-standard for inhalation aerosols and was developed by CCL and its affiliates and is referenced on pages 00662-00697 in the original ANDA submission of December 23, 1988. Additional test data and a revised test method were submitted as pages 261-441 of the 4/30/90 amendment.

The [redacted] is used to evaporate all the propellants from the aerosol cloud, resulting in drug particles only entering the laser beam. The [redacted] to approximately [redacted] to ensure evaporation of propellants occurs. The measurements are based on drug and surfactant only and are not a measurement of droplet size. This unique method provides a uniform background (free of evaporation of propellants) from which it is possible to make a more stable measurement.

The . . is placed cm away from the lens to ensure that all particles are measured. If the pipe is placed further than cm away from the lens then vignetting occurs, this results in smaller particles diffracting the laser to such an extent that they miss the detecting rings, this results in an inaccurate measurement.

The canisters are sprayed at an angle to allow the drug product to descend the downpipe. This angle would have no effect on the results as the drug would exit the aerosol in exactly the same manner as it would in the upright position.

The effect of spraying every 2-5 seconds and not as directed on the labeling would not be expected to have an effect on the results obtained. Rapid firing of the unit should result only in minor variations in dosage and drug particle size. The effects of reduced propellant evaporation caused by valve cooling from rapid firing are likely to be offset by the heated downpipe. The dose delivered has no effect on this method as we do not need to quantify the amount of drug delivered in the method.

12. **Regarding the twin stage impinger study (Volume A8.2, pp. 606-615), please provide the amount of drug in both the upper and lower stages for each canister, and the average shot dose as determined by In addition, please provide respirable fraction for each canister for the data tabulated on p. 615, as defined in USP 23 <601>, Single-stage Impactor Apparatus 2.**

The amount of drug in the upper and lower stages is provided on pages 162 and 163. The average shot dose and respirable fraction and respirable percent are also provided.

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that the field copy is a true copy of this amendment to the application and has been sent to the FDA Baltimore District Office.

We trust that we have addressed the Agency's concerns.

Sincerely,
A.L. Laboratories, Inc.

Ronald Begnum / for

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure

A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
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AMENDMENT
N/AM

May 1, 1996

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MAY 0 2 1996
GENERIC DRUGS

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96(a), A. L. Laboratories submits an amendment to the above referenced application. Reference is made to the Agency's letter dated April 8, 1996 (attached), regarding our Abbreviated New Drug Application dated December 28, 1988, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Agency's comments have been restated and our responses follow.

1.

DMF remains deficient. Please request them to respond to all outstanding deficiencies cited by the FDA letter dated March 11, 1996. Please be advised that all the deficiencies must be resolved prior to approval of this application.

the DMF holder has indicated that they responded to their DMF deficiencies on April 29, 1996 (page 2).

5-9-96

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2.

A satisfactory compliance evaluation is required prior to approval of the ANDA.

The drug product manufacturing facility (CCL Industries Ltd.) and its contract laboratory underwent FDA's pre-approval inspections between April 15 to April 17, 1996, and April 23 to April 25, 1996, respectively. The FDA inspectors indicated that based on their inspections, they would recommend approval of the application.

We trust that we have addressed the Agency's concerns.

Sincerely,
A.L. Laboratories, Inc.

Deborah Miran
Sr. Director, Regulatory Affairs

DM/rb

Enclosure

A. L. LABORATORIES, INC.
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NEW CORRES
NC

March 27, 1996

Jim Allgire
Division of Drug Analysis
Food and Drug Administration
1114 Market Street
St. Louis, MO 63101

MAR 28 1996

Re: ANDA #73-045
Albuterol Inhalation Aerosol, 90 µg/Inhalation

Dear Mr. Allgire:

Per the March 21, 1996 teleconference between yourself and Mr. Ronald Bynum of A. L. Laboratories, enclosed please find a copy of the analytical methods for drug product release and drug product stability testing. Also enclosed are samples of the drug product and the non-compendial reference standard utilized in the Related Substance test. All other reference standards are compendially sourced, and are therefore not included.

The drug product release methods have method numbers beginning with The drug product stability methods have method numbers beginning with Please note that the same basic method is used for both drug product release and stability testing.

120 canisters of Albuterol Inhalation Aerosol, batch number 8457, manufactured by CCL Industries, have been included. This batch was manufactured in November, 1995 and will expire in December, 1997. These canisters do not contain paper labels since the labeling operation has not been conducted at this time. The canisters are marked as follows:
ALB 8457
XXXXX

ALB identifies the product as Albuterol Inhalation Aerosol.

8457 identifies the product batch number.

XXXXX indicates the sequential number of the filled canister. In addition, the canisters have been denoted with blue ink as being from the start of the process ("S"), the middle of the process ("M"), or the end of the process ("E").

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120 actuators are also provided.

A sample of the reference standard for the Related Substance 1-4(Hydroxy-3-Methylphenyl)-2-(Tertbutylamino)Ethanol is also included. An additional quantity of this Related Substance reference standard is on order, and if necessary, will be sent to your office upon receipt.

If you have any questions upon receipt of these samples or during the testing of same, then please contact Mr. Ronald Bynum at 410-558-7250 (phone) or 410-558-7258 (fax).

Sincerely,

A.L. Laboratories, Inc.

Ronald Bynum /for
Deborah Miran
Sr. Director, Regulatory Affairs

DM:rb

enclosure

cc: Nancy Haggard, Int'l. & Tech. Oper. Br. (Rm 12-18, HFD-134)
Douglas Sporn (for ANDA # 73-045), OGD (MPN II, Rm 150)

A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
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February 23, 1996

Office of Generic Drugs
CDER, FDA
Attn: Charles Ganley, MD, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA # 73-045**
ALBUTEROL INHALATION AEROSOL, 90 MCG/INHALATION

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Dr. Ganley:

Pursuant to 21 CFR 314.96 (a)(1), A. L. Laboratories submits an amendment to its pending abbreviated application of December 23, 1988. Reference is made to the Administration's letter of January 29, 1996 (attached). Reference is also made to the Administration's correspondence of July 12, 1991, June 3, 1994, August 11, 1994 and May 26, 1995, and to A.L.'s correspondence of February 4, 1994, February 14, 1994, December 2, 1994, January 27, 1995, June 12, 1995, June 22, 1995, and August 1, 1995. The Administration's comments from the January 29,1996 correspondence have been restated and A.L.'s responses follow.

Chemistry Deficiencies:

1. **DMF [ ] remained deficient. Please request them to respond to all outstanding deficiencies cited by the FDA letter dated November 22, 1995. Please be advised that all the deficiencies must be resolved prior to approval of this application.**

[ ] has indicated that FDA's November 22, 1995 deficiency letter to DMF [ ] pertained to deficiencies in the DMFs [ ] held by the manufacturer of intermediate ingredients [ ] responded to the deficiencies in DMFs [ ] on December 28, 1995.

A copy of a letter from [ ] indicating the response to the deficiency letter is enclosed as page 02. [ ] has indicated to us that all the deficiencies have been addressed.

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2. Please revise your specifications for Propellant-11 and Propellant-12 per CDER's current requirements. ... Please commit to put through these specifications within six months post-approval of this ANDA. You may submit a "Special Supplement - Changes Being Effected" with your results and methods validation to detect all the impurities.

A.L. Laboratories commits to establishing specifications for detection of impurities in Propellant-11 and Propellant-12 per CDER's current requirements. A.L. Laboratories further commits to filing the specifications, methods, methods validation, and analytical test results to the application post-approval in a "Special Supplement - Changes Being Effected" submission no later than six months after approval of the application.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. Please be advised that we have instructed the FDA's International and Technical Operations Branch to collect samples of the drug product from the manufacturing facility of the drug product (ie., CCL Industries, England) for the validation of the analytical methods. A satisfactory methods validation is required prior to approval of this ANDA.

A.L. Laboratories acknowledges that samples of the drug product will be collected from the manufacturing facility of the drug product and that satisfactory methods validation is required prior to approval of this ANDA.

2. A satisfactory compliance evaluation is required prior to approval of the ANDA.

A.L. Laboratories acknowledges that a satisfactory compliance evaluation is required prior to approval of this ANDA.

In addition to responding to the Administration's concerns, A.L. Laboratories is also providing updated information to this application.

Updated drug product room temperature stability summaries with data from the 24 months stability test station are provided as pages 03-06. Data from both the inverted orientation (valve down) and the upright orientation (valve up) are provided. The previous room temperature stability summaries were submitted as pages 75-83 of the 8/1/95 amendment to the application.

An updated listing of component sources for the drug product is enclosed as pages 07-08. ( ) has been added as a new manufacturer of Propellant 11 and Propellant 12. The previous listing of drug product component sources was submitted as pages 24-25 of the 2/4/94 amendment to the application.

Updated analytical procedures and an explanation of the changes for the Metering Performance test and the Deposition of Emitted Dose (Twin Impinger test are enclosed as pages 09-10 and 11-19, respectively.

Pursuant to 21 CFR 314.96(b), A.L. Laboratories certifies that a field copy, a true copy of this amendment to the application, has been sent to the FDA Baltimore District Office.

We trust that our responses fully address the Administration's concerns.

Sincerely,

A.L. Laboratories, Inc.

Vincent Andolina
for

Deborah Miran
Senior Director, Regulatory Affairs

enclosure

DM:rb

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A. L. LABORATORIES, INC.
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BIOAVAILABILITY

AMENDMENT N/AC

August 1, 1995

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA #73-045
Albuterol Inhalation Aerosol, 90 mcg / Inhalation

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn,

Pursuant to 21 CFR 314.96 (a) (1), A. L. Laboratories submits an amendment to its pending abbreviated application of December 28, 1988. Reference is made to the Administration's letter of May 26, 1995. Reference is also made to the Administration's correspondence of July 12, 1991 and August 11, 1994 and to A.L.'s correspondence of February 4, 1994, December 2, 1994, and January 27, 1995. The Administration's comments from May 26, 1995 have been restated and A.L.'s responses follow.

A. Chemistry Deficiencies:

1. **DMF is deficient. Please request them to respond to all outstanding deficiencies cited by the recent FDA letter. Please be advised that all deficiencies must be resolved prior to approval of this application.**

   has indicated that on June 28, 1995 they responded to all outstanding DMF deficiencies cited in the May 1, 1995 FDA letter (page 02).

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2. **Please be advised that stability should be conducted in both orientations of the container/closure system (upright/inverted) in accordance with the current CDER Stability Guideline. According to your post-approval stability protocol, you plan to conduct stability studies only on samples stored in the inverted position. Please revise your post-approval stability testing protocol such that upright samples are tested at zero time and annually. Furthermore, please also revise your stability testing protocol to reflect storage conditions of 25° - 30°C at ambient humidity in accordance with the current requirements of this Office.**

   A post-approval stability protocol has been developed for testing of the drug product in the upright (valve up) orientation (pages 03-04). The post-approval stability protocols for both the upright and the inverted orientations have been revised to reflect storage temperatures of °C at ambient humidity (pages 03-04 and 05-06, respectively).

B. Labeling Deficiencies:

Insert

The insert labeling has been revised as requested and new final printed insert labeling is enclosed as page 07.

C. Bioequivalence Deficiencies

Bioequivalency of this product has not been established. An appropriate study has not been submitted.

A. L. Laboratories submitted the bioequivalency study on June 12, 1995.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. **Please be advised that a satisfactory methods validation is required prior to approval of this ANDA. We will request that the method validation study be initiated when your bioequivalence study is submitted.**

   A. L. Laboratories acknowledges that satisfactory methods validation is required prior to approval of the application. In response to the above reference that the methods validation study would not be initiated until the bioequivalence study was submitted, A. L. Laboratories restates that the bioequivalence study was submitted on June 12, 1995.

2. **A satisfactory compliance evaluation is required prior to approval of the ANDA. We will request an evaluation when your bioequivalence study is submitted.**

   A. L. Laboratories acknowledges that a satisfactory compliance evaluation is required prior to approval of the application. In response to the above reference that the compliance evaluation would not be requested until the bioequivalence study was submitted, A. L. Laboratories restates that the bioequivalence study was submitted on June 12, 1995.

At this time, A. L. Laboratories would like to report on the up-dating of documentation for this application:

The Content Uniformity test was revised to incorporate the labeling requirement of two sprays per dose (pages 09-12 for drug product release and pages 13-17 for drug product stability). The Content Uniformity specification was revised to comply with the USP requirement for aerosols (pages 03-06 for post-approval and pages for pre-approval). The previous test method was submitted as pages 073-076 (release testing) and 110-113 (stability testing) of the 12/2/94 amendment to the application.

The revised Content Uniformity test method was used in the stability testing at the 18 months room temperature stability test stations (page 79 for inverted orientation and page 82 for upright orientation). The results conform to the product specifications. In addition, the revised Content Uniformity test was evaluated for precision and found to be superior to the previous method (pages 18-33).

A separate Unit Spray Content test was added to monitor drug delivered from the start, middle, and end of the can for both QC release testing and stability testing (pages 35-38 and 39-43, respectively).

The new Unit Spray Content test method was used in the stability testing at the 18 months room temperature stability test stations (page 79 for inverted orientation and page 83 for upright orientation)).

The Total Number of Shots (Actuations per can) test was revised to be conducted during the Unit Spray Content test rather than during the Content Uniformity test.

Due to the change in the Content Uniformity test and the addition of the Unit Spray Content test, and the update to USP 23 tests, the Product Specification and the Pre-Approval Stability Protocols and the Post-Approval Stability Protocol were revised.

✓ Post-Approval Stability Protocol 25°C/ambient humidity, Upright (pages 03-04).
Post-Approval Stability Protocol 25°C/ambient humidity, Inverted (pages 05-06).
Product Specification (pages 45-47).
Stability Monograph (pages 48-49).
Pre-Approval Stability Protocol 40°C/85% RH, Inverted (pages 50-52).
Pre-Approval Stability Protocol 40°C/85% RH, Upright (page 53).
Pre-Approval Stability Protocol 25°C/60% RH, Inverted (pages 54-56).
Pre-Approval Stability Protocol 25°C/60% RH, Upright (page 57).

The previous specifications and protocols were submitted as pages 048-049 and 213-234, respectively of the 12/2/94 amendment to the application.

The analytical method "Amount Retained On The Oral Adaptor" was revised into the current document format (pages 60-62). The previous revision of the method was submitted as pages 615-617 of the 2/4/94 amendment to the application.

The analytical method "Related Substances And Extractables[ ]was revised into the current document format (pages 65-69). The previous version of the method was submitted as pages 141-144 of the 12/2/94 amendment to the application.

The analytical method "Content Of Albuterol Per Can" was revised into the current document format (pages 72-74). The previous version of the method was submitted as pages 589-591 of the 2/4/94 amendment to the application.

The stability summaries have been updated to include results from the 18 months test station. In addition, the summaries have been revised to include corrections of results based on an internal audit of data in which the calculations were re-performed on the raw data. The format of the stability summaries has been changed to a horizontal presentation from a vertical presentation. The stability summaries for the room temperature studies were revised to list the current specification for each test.

25° C, inverted (pages 75-80).
25° C, upright (pages 81-83).
40° C, inverted (pages 84-86).
40° C, upright (pages 87).

The room temperature stability data for the inverted orientation canisters were previously submitted to the application as pages 261-262 of the 12/2/94 amendment to the application and page 264 of the same amendment contained data for the upright orientation canisters. The accelerated stability data for the inverted orientation canisters were previously submitted to the application as page 621 of the 2/4/94 amendment to the application and page 625 of the same amendment contained data for the upright orientation canisters.

Pursuant to 21 CFR 314.96 (b), A.L. Laboratories certifies that a field copy of this amendment to the application has been submitted to the FDA District Office.

Sincerely,
A.L. LABORATORIES, INC.

Deborah Winkel
Sr. Director, Regulatory Affairs

DW/rb

Enclosure

ORIGINAL

BIOAVAILABILITY

A. L. LABORATORIES, INC.
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Bio in MIS
D Knight 8/7/95

June 22, 1995

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG NEW SUBMISSION

RE: ANDA #73-045
Albuterol Inhalation Aerosol, 90 µg/Actuation

AMENDMENT - BIOEQUIVALENCE INFORMATION

Dear Mr. Sporn:

Reference is made to our June 12, 1995 amendment to pending application of the in-vivo bioequivalence study and the in vitro comparative data for Albuterol Inhalation Aerosol.

Enclosed are the Individual FEV_1 Efforts for the Bronchoprovocation Study for patients that were screened but not entered in the study. This response was discussed with Mr. Wallace Adams of your office.

We trust that our response fully addresses the Administration's concerns.

Sincerely,

A. L. LABORATORIES, INC.

Deborah Winkel,
Sr. Director, Regulatory Affairs

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JUN 26 1995

enc.

The Johns Hopkins Bayview Research Campus
333 Cassell Drive, Suite 3500 • Baltimore, Maryland 21224
Telephone: 410 558-7250 • Fax: 410 558-7262

A. L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
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Bio In Mis. Dkmgate 6/26/95

June 12, 1995

NEW CORRESP
BIOAVAILABILITY

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Douglas Sporn, Acting Director
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA #73-045
Albuterol Inhalation Aerosol, 90 µg/Actuation

AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn,

Pursuant to 21 CFR 314.96 (a) (1) and 21 CFR 314.94 (a) (7), A. L. Laboratories submits an amendment to its pending application by providing the *in-vivo* bioequivalence study and the in vitro comparative data for Albuterol Inhalation Aerosol. Reference is also made to the Interim Guidance For Documentation of *In* Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers) issued January 27, 1994 and the Guidance for the In Vitro Portion of Bioequivalence Requirements for Metaproterenol Sulfate and Albuterol Inhalation Aerosols (Metered Dose Inhalers) issued on or about June 27, 1989. Lastly, reference is made to the Administration's letter of June 3, 1994 pertaining to our February 14, 1994 Bio-IND submission (Bio-IND and to our ANDA submitted December 23, 1988. This amendment consists of two volumes. The *in-vivo* section is contained in Volume 1 and the in-vitro section is contained in Volume 2.

Responses to the Administration's June 3, 1994 comments pertaining to Bio-IND' are contained on pages 004-007. In addition, the information required under 21 CFR 312.33 pertaining to IND Annual Reports is contained within the bioequivalence report (pages 025-251). The Annual report information has not been submitted separately since the protocol was concluded within approximately 60 days of the Bio-IND anniversary date.

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JUN 14 1995
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The Johns Hopkins Bayview Research Campus
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Enclosed is the *in-vivo* bioequivalence study entitled A Bronchoprovocation Study Comparing Two Formulations Of Albuterol Metered-Dose Aerosol Inhaler In Patients With Mild To Moderate Asthma (Protocol #10647) (pages 025-251) and the safety study entitled Safety Evaluation Of Two Formulations Of Albuterol Metered Dose Aerosol Inhaler In Healthy Volunteers (Protocol #10667) (pages 252-478). The bioequivalence study results are also provided on a computer diskette. A hard copy of the data contained on the computer diskette is provided as pages 010-024.

Per the in vitro guidance, a copy of the executed batch record for Albuterol Inhalation Aerosol, lot #6403 is enclosed (pages 479-556). The batch record was previously submitted as pages 219-293 of the 2/4/94 amendment. As noted on pages 6-7 of the response in the 2/4/94 amendment, some portions of the batch record indicate the batch number as #403, or ALB 6403, or #6403 - however, all records pertain to the same batch, only the nomenclature of the batch number is different.

Also enclosed is the in vitro comparative data between the test drug product (Albuterol Inhalation Aerosol, batch #6403 and the reference drug product (Ventolin® Inhalation Aerosol (batch #Z31383LS) (pages 557-627).

The in vitro portion of the bioequivalence requirements contains particle size testing by cascade impaction (pages 557-567), particle size testing by laser diffraction (pages 568-605), particle size testing by twin impinger (pages 606-615), spray pattern testing (pages 616-620), and potency testing (pages 621-627).

Particle size analysis was not performed by microscopic examination. Instead, two alternative procedures (Malvern Laser and Deposition of Emitted Dose via Twin Impinger) were used for particle size analysis. The two alternative procedures provide a more accurate and definitive measure of overall particle size distribution of albuterol and fine particle fraction required for an inhalation aerosol. Cascade Impaction was also utilized giving further data on particle size distribution of the aerosol. The in vitro guidance requires particle size testing by two different test methods, we are supplying particle size testing from three different test methods.

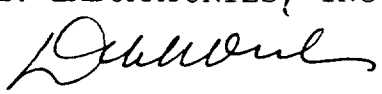
Plume geometry testing was not performed since it is believed that no quantitative data or conclusions can be made from comparative photographs of aerosol clouds. The basis of an equivalent claim is more appropriately made on deposition of dose delivered and spray pattern.

Per the in vitro guidance, a copy of the executed batch record for Albuterol Inhalation Aerosol, lot #6403 is enclosed (pages 628-705. The batch record was previously submitted as pages 219-293 of the 2/4/94 amendment. As noted on pages 6-7 of the response in the 2/4/94 amendment, some portions of the batch record indicate the batch number as #403, or ALB 6403, or #6403 - however, all records pertain to the same batch, only the nomenclature of the batch number is different.

In addition, a study comparing potency delivered through the mouthpiece (Single Spray Drug Content Of US Brand Leader vs DF31 Following A Collection Scheme Approximating Actual Usage) is also enclosed (pages 706-736). The conclusion of this comparative potency study is that drug delivery through the aerosol valve on the A. L. product is equivalent to or better than that for the aerosol valve used in Ventolin® Inhalation Aerosol (Glaxo). This study was previously submitted to the application as pages 637-667 of the 2/4/94 amendment to the application. The study is being resubmitted at this time since it provides information on comparative in vitro characteristics between the test drug product and the reference drug product.

Sincerely,

A.L. LABORATORIES, INC.



Deborah Winkel
Sr. Director, Regulatory Affairs

A.L. LABORATORIES, INC.
U.S. PHARMACEUTICAL GROUP
RESEARCH • DEVELOPMENT • REGULATORY

January 27, 1995

Office of Generic Drugs
CDER, Food and Drug Administration
Attn: Mr. Douglas Sporn, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

n/pc

Re: **ANDA #73-045**
ALBUTEROL INHALATION AEROSOL, 90 mcg / INHALATION

AMENDMENT TO THE DECEMBER 2, 1994
MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96 (a) (1), A.L. Laboratories herewith submits an amendment to its above referenced pending abbreviated new drug application. Reference is made to Observation A. 4. c. from the Agency's letter dated August 11, 1994 (attached) requesting temperature cycle data and our response dated December 2, 1994. In addition, reference is made to the Agency's letter dated July 21, 1991 and our correspondence dated July 26, 1993 and February 4, 1994 and December 2, 1994.

The Agency's comments from Observation A. 4. c. have been restated and A.L's response follows.

A. Chemistry Deficiencies:

4. We have the following comments regarding the stability of the drug product:

c. Please submit results of temperature cycling studies conducted for the exhibit batch in accordance with the CDER Stability Guideline.

A temperature cycle study has been performed on the exhibit batch and the results are summarized on page 2. The drug product samples were cycled

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for six weeks between temperatures of °C at six hour intervals. Results for the reference drug product, Ventolin Inhalation Aerosol, lot number 4ZPA107 are provided for comparison purposes (page 3). The reference drug product was cycled simultaneously with the Albuterol Inhalation Aerosol test drug product.

A.L. Laboratories certifies that a field copy of this amendment has been submitted to the FDA district office pursuant to 21 CFR 314.96 (b).

We trust that this response has addressed the Administration's concerns.

Sincerely,
A. L. LABORATORIES, INC.

Deborah Winkel
Sr. Director, Regulatory Affairs

Enclosure

ORIGINAL

A.L. LABORATORIES, INC.
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December 2, 1994

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ALBUTEROL INHALATION AEROSOL, 90 mcg/INHALATION

MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

Pursuant to 21 CFR 314.96, A.L. Laboratories herewith submits an amendment to its above referenced pending abbreviated new drug application. Reference is also made to the Agency's letter dated August 11, 1994 (attached). In addition, reference is made to the Agency's letter dated July 21, 1991 and our correspondence dated July 26, 1993 and February 4, 1994.

The Agency's comments have been restated and our responses follow.

A. Chemistry Deficiencies:

1. Please revise your specifications for Oleic Acid in accordance with the NF monograph with respect to acid, saponification and iodine values.

Test	CCL Specification	NF Specification
Acid Value		
Iodine Value		
Saponification Value		

CCL's specifications are joint specifications for USP/NF and BP. The above Oleic Acid tests utilize the BP specifications since the BP specifications are tighter than the NF specifications, but yet are still within the NF specifications. CCL will continue to utilize the tighter specifications as long as they are within the NF specifications.

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